Large Granular Lymphocyte Expansion after Allogeneic Hematopoietic Stem Cell Transplant Is Associated with a Cytomegalovirus Reactivation and Shows an Indolent Outcome

Sabine Nann-Rütti,[1] Alexander Tzankov,[2] Nathan Cantoni,[1] Jörg Halter,[1] Dominik Heim,[1] Dimitrios Tsakiris,[1] Caroline Arber,[1] Andreas Buser,[1] Alois Gratwohl,[1] André Tichelli,[1] Alicia Rovó[1]

Expansions of CD3+ large granular lymphocytes (LGLs) after allogeneic hematopoietic stem cell transplantation (HSCT) have been described. We sought to evaluate incidence, characteristics, and clinical significance of persistent T cell (T-)LGL after HSCT. Fourteen of 215 recipients (7%) were diagnosed with LGL expansions. Thirteen showed a CD3+/CD8+ immunophenotype, 5 of them with clonal TCR-γ rearrangement. The lymphocytes appeared at a median of 16 months (range, 3-58 months) after HSCT and lasted for a median time of 31 months (range, 2-179 months). Cytomegalovirus (CMV) reactivation ($P = .001$) and acute graft-versus-host disease (aGVHD) were associated with LGL expansion ($P = .02$). In the multivariate analysis, only CMV reactivation showed a significant association with T-LGL expansion (relative risk [RR]: 5.063; 95% confidence interval [CI]: 1.586-16.160; $P = .006$). The observed posttransplantation LGL expansions, even if monoclonal, showed a chronic, indolent course. Our data indicate that such expansions may be considered as an expression of chronic stimulation, triggered by CMV reactivation rather than a malignant transformation.

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INTRODUCTION

Large granular lymphocytes (LGLs) are immunophenotypically heterogeneous lymphocytes. Immunophenotypically, they can be either CD3-negative natural killer cells (NK-LGL) or activated CD3-positive cytotoxic T cells (T-LGL), the latter usually accounting for less than 5% of all lymphocytes in a normal peripheral blood [1]. Reactive expansions of T-LGL can occur within different situations such as autoimmune diseases, underlying malignant neoplasms [2], viral infections [3], especially cytomegalovirus (CMV) infection [4,5], or after therapy with tyrosine kinase inhibitors in patients with chronic myeloid leukemia [6]. Reactive T-LGL expansions are usually polyclonal, transient, and asymptomatic. Neoplastic clonal proliferation of T-LGL is classified as T cell large granular lymphocytic leukemia in the World Health Organization classification [7,8]. T-LGL leukemia is characterized by a persistent increase of the number of peripheral blood LGL, usually between 2 to 20 $\times$ 10^9/L without a clearly identified cause [8]. However, it is now recognized that a lower count (range, 0.4-2 $\times$ 10^9/L) may be compatible with the diagnosis [9]. After allogeneic hematopoietic stem cell transplant (HSCT), T-LGL expansions have been described [10,11]; however, data about characteristics and clinical outcome of patients with LGL populations after allogeneic HSCT are still sparse. Therefore, we aimed to evaluate frequency, clinical presentation, laboratory features, outcome, and risk factors of patients with a persistent T-LGL population after allogeneic HSCT.

METHODS

This was a single-center, cross-sectional study performed at the Hematology Division of the University of Basel, Switzerland. After allogeneic HSCT, all recipients were regularly controlled at 1, 3, 6, and 12 months, and thereafter at yearly intervals or more often when indicated. These consultations included assessment of medical history, physical examination, and laboratory tests, such as complete blood count including morphological analysis of peripheral blood cells, lymphocyte subpopulations, peripheral blood chimerism, and blood chemistry. Bone marrow

From the [1]Department of Hematology; and [2]Department of Pathology, University Hospital of Basel, Basel, Switzerland.

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Correspondence and reprint requests: Alicia Rovó, MD, University Hospital of Basel, Department of Hematology, Petersgraben 4, CH-4031 Basel, Switzerland (e-mail: RovoA@uhbs.ch).

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(BM) investigation was performed regularly at 3 and 6 months, at 1, 2, and 5 years, and every 5 years thereafter. During the first 90 days after HSCT, additional monitoring of immunosuppression and CMV replication using pp65 antigenemia or real-time PCR was done as described in a previous study [12].

In this study, all postallogeneic HSCT recipients who came to regular controls between January 1, 2008, and December 31, 2009, were consecutively included. On control day, in accordance with our standards, previous blood counts were reviewed: if patients showed persistent lymphocytes (>3 G/L for more than 3 months) and abnormal CD4/CD8 ratios in the lymphocyte subpopulations, defined as CD4/CD8 <1.0 or >1.5, and extensive immunophenotyping of the peripheral blood cells was assessed. Flow cytometry analyses were performed using the flow cytometry system FACSCalibur (BD Biosciences, San Jose, CA). The immunophenotyping of the lymphocytes included the following antibody panel: CD2, CD3, CD4, CD5, CD7, CD8, CD16, CD25, CD30, CD56, CD57, HLA-DR, TCRαβ, and TCRγδ. T-LGL expansion was defined as an abnormal T cell population type CD3+, CD8+, or CD4+, with expression of at least 1 of the NK markers (CD16, CD57, or CD56), and with presence of LGLs in peripheral blood films [13]. In all cases with an abnormal expansion of T-LGL cells, a TCR gene rearrangement from peripheral blood or BM was performed (4 color multiplex PCR assay and automated high-resolution fragment analysis on ABI 310 Genetic Analyzer; Applied Biosystems, Foster City, CA).

We compared patients with T-LGL expansion to the cohort of patients without LGL expansion, using the chi-square test for categorical data and the Mann-Whitney *U* test for continuous variables. Variables included into the analysis were age, sex, diagnosis (malignant versus nonmalignant diseases), conditioning regimen (myeloablative versus reduced intensity conditioning), total body irradiation (TBI), type of donor, graft source, acute graft-versus-host disease (aGVHD) or chronic GVHD (cGVHD), remission status at control, and CMV reactivation. To identify independent prognostic risk factors, a multivariate stepwise linear regression analysis was performed. Differences between the results of comparative tests were considered significant if the 2-sided *P* value was <.05. Statistical analysis was performed using SPSS statistical software (SPSS for Windows, Release 17, SPSS, Inc., Chicago, IL).

Patients provided a written informed consent to have their data on disease, treatment, and outcome including late complications reported in an anonymous way to the registry. Clinical surveillance of HSCT recipients was approved by local institutional review boards. Patient characteristics, HSCT conditioning regimens, and clinical outcome data were collected prospectively and stored in the local institution database registry.

RESULTS AND DISCUSSION

Within 215 post-HSCT evaluated patients, 14 (7%) had an LGL expansion. Patients' characteristics with and without LGL expansion are summarized in Table 1. Primary disease, remission status, and HSCT characteristics of patients with LGL expansion are detailed in Table 2. The median time between HSCT and the beginning of lymphocytes, and between HSCT to study time was 16 months (range, 3-58 months) and 56 months (range, 3-159 months), respectively. The median lymphocyte count was 4.24 G/L (range, 3.0-26.5 G/L), and the median count of the T-LGL population was 2.10 G/L (range, 1.25-11.52 G/L) (Table 3). The median duration of the lymphocytes was 31 months (range, 2-179 months). The immunophenotyping in all these patients showed a T-LGL proliferation. In 13 of 14 patients, the following phenotype was found: CD3+, CD8+, CD4-, CD2+, CD5+, CD7+, and TCRαβ+. From these 13 patients, 7 expressed CD16+ CD57+; 5 expressed CD57+; and 1 expressed CD16+, CD56+ and, CD57+. In 1 of the 14 patients, the population was CD3+, CD4+, CD8-, additionally expressing CD2+, CD5+, CD7+, CD56+, CD57+, and TCRαβ+. The TCR-γ gene rearrangement examination was performed in all 14 patients (from peripheral blood in 8 of 14 patients [57%]; and from BM in 6 of 14 patients [43%]). In 5 patients, clonality was found (1 patient showed biclonality). Detailed descriptions of patients' characteristics with LGL expansion are summarized in Table 3.

Neutrophil counts were normal in all patients with LGL expansion. Eight of 14 patients (57%) showed a mild hyporegenerative anemia. Thrombocytopenia was present in 2 of 14 patients (14%) (1 associated with graft rejection, and 1 associated with CMV infection). Five of 14 recipients showed elevated antinuclear antibodies, 4 of them with a slight increase and 1 with a moderate increase. One patient had elevated rheumatoid factors, 2 patients had mild hypergammaglobulinemia, 3 patients had minimal M-gradient, and 1 patient had a mild positive polyspecific antiglobulin test for IgG without clinical evidence of hemolysis, as well as a monoclonal IgG λ of 7 g/L.

At the time of diagnosis of LGL expansion, 1 patient had persistent disease (primary myelofibrosis) and the chimerism was recipient type. This patient never engrafted after umbilical cord blood transplantation. The other 13 patients had a complete hematological remission with 100% donor type chimerism in peripheral blood. One of these 13 patients had a BCR-ABL1 molecular relapse of a B lymphoblastic leukemia at study time. Three patients were

Table 1. Characteristics of Patients Treated with Allogeneic HSCT, Presenting with or without T-LGL

	Total	With T-LGL Expansion	Without T-LGL Expansion	*P* Value
No. of patients	215	14	201	
Median age at HSCT, years (range)	41 (12-68)	38.5 (25-64)	41 (12-68)	.835
Median age at follow-up, years (range)	48 (21-70)	45 (30-70)	48 (21-69)	.519
Sex				
Male	124 (58%)	7 (50%)	117 (58%)	.548
Female	91 (42%)	7 (50%)	84 (42%)	
Diagnosis				
Malignant hematological diseases	202 (94%)	13 (93%)	189 (94%)	.814
Aplastic anemia	10 (4%)	1 (7%)	9 (4%)	
Autoimmune disease	3 (2%)	0	3 (2%)	
Conditioning				
Myeloablative	174 (84%)	11 (79%)	163 (85%)	.528
Reduced intensity conditioning	32 (16%)	3 (21%)	29 (15%)	
TBI				
No TBI	61 (28%)	3 (21%)	58 (29%)	.551
With TBI	154 (72%)	11 (79%)	143 (71%)	
Donor				
Matched related	139 (65%)	9 (64%)	130 (65%)	.319
Matched unrelated donor	63 (29%)	3 (21%)	60 (30%)	
Mismatched donor*	10 (5%)	2 (14%)	8 (4%)	
Syngeneic sibling	3 (1%)	0	3 (1%)	
Graft				
Peripheral blood stem cells	159 (78%)	10 (72%)	149 (79%)	.550
Bone marrow	43 (21%)	3 (21%)	40 (21%)	
Cord blood	1 (1%)	1 (7%)	0	
CMV reactivation				
No	143 (73%)	5 (36%)	138 (76%)	.001
Yes	52 (27%)	9 (64%)	43 (24%)	
GVHD				
aGVHD grade 0-1	112 (55%)	4 (29%)	111 (57%)	.02
aGVHD grade 2-4	93 (45%)	10 (91%)	83 (43%)	
No cGVHD	62 (29%)	4 (29%)	58 (29%)	.610
cGVHD	150 (71%)	10 (71%)	140 (71%)	
Remission status at control				
Complete remission	92 (84%)	13 (93%)	79 (83%)	.350
Not in complete remission	17 (16%)	1 (7%)	16 (17%)	
Follow-up (days)	223 (92-971)	316 (195-658)	217 (92-971)	.007

HSCT indicates hematopoietic stem cell transplant; T-LGL, T cell large granular lymphocyte; TBI, total body irradiation; CMV, cytomegalovirus; GVHD, graft-versus-host disease; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease.
*Inclusively cord blood donor.

affected by joint pain that had appeared previously and was considered to be associated with cGVHD. No patient showed palpable splenomegaly, and none of them had typical signs or symptoms of an autoimmune disease. Previously mentioned cytopenias were considered linked to transplant-related problems rather than associated with the LGL expansion. BM biopsy was evaluable in 13 of 14 patients. The majority of patients presented with a hypocellular BM (7 of 13 patients); it was normocellular in 3 and hypercellular in another 3 patients. The extension of BM involvement through T cells was far less than 50% of all cellular elements. None of the patients fulfilled the diagnostic criteria for LGL leukemia according to the World Health Organization classification [8]. None of the patients had an indication for therapy due to LGL expansion.

In univariate analysis, patients with LGL presented more often with a history of CMV reactivation ($P = .001$) and of aGVHD ($P = .02$), when compared with patients without LGL. In multivariate analysis, CMV reactivation (relative risk [RR]: 5.063; 95% confidence interval [CI]: 1.586-16.160; $P = .006$), but not aGVHD (RR: 2.831; 95% CI: 0.831-9.648; $P = .096$), showed a significant association with LGL expansion. Age of the patient, conditioning regimen, donor type, graft source, and initial diagnosis as well as relapse after HSCT were not related to T-LGL expansion.

Our data show that persistent LGL expansion after allogeneic HSCT is not a rare finding and appears in nearly 1 of 10 patients during the follow-up. In contrast, reports on LGL expansion after autologous HSCT are scarce [14]. Patients with LGL expansion were clinically asymptomatic, despite showing discrete biological changes. The high frequency of LGL expansions after HSCT is consistent with the unique previous series published by Mohty et al. [15], with 6 cases of LGL expansion in a cohort of 201 patients. However, Mohty et al. [15] showed different findings with respect to clinical presentation. Indeed, 4 of 6 patients with T-LGL

Table 2. Characteristics of Patients with LGL Expansion

Patient	Sex	Age at HSCT (Years)	Diagnosis to HSCT	Disease Status at HSCT	Type of Donor	Graft Source	CD34+ (×10e6/kg)	Conditioning	TBI (Yes/No)	Doses (Gy)	GVHD Prophylaxis
8	Male	64	AML	Persistent MDS	Matched related	Peripheral blood	4.8	Reduced intensity	Yes	2	CyA/MMF
6	Female	25	SAA	Refractory after ATG	Matched unrelated	BM	3.6	Reduced intensity	Yes	1	CyA/MTX
12	Male	42	AML	2nd CR	Mismatched unrelated	Peripheral blood	7.6	Myeloablative	Yes	12	CyA/MTX
9	Male	46	ALL	2nd CR	Matched unrelated	Peripheral blood	6.0	Myeloablative	No		CyA/MTX
13	Female	30	NK/TL	2nd CR	Matched related	Peripheral blood	6.8	Myeloablative	Yes	2	CyA/MMF
1	Female	27	CML	Accelerated phase	Matched related	BM	4.8	Myeloablative	Yes	12	CyA/MTX
2	Male	37	CML	1st chronic phase	Matched unrelated	BM	3.2	Myeloablative	Yes	12	CyA/MTX
3	Female	49	CML	2nd chronic phase	Matched related	Peripheral blood	5.3	Myeloablative	Yes	12	CyA/MTX
5	Male	30	DLBCL	Progression	Matched related	Peripheral blood	6.1	Myeloablative	Yes	2	CyA/MMF
7	Male	40	ALL	Partial remission	Matched related	Peripheral blood	3.6	Myeloablative	Yes	12	CyA/MTX
10	Female	41	CLL	2nd CR	Matched related	Peripheral blood	7.5	Myeloablative	Yes	2	CyA/MMF
11	Female	37	PMF	Progression	5/6 matched cord	Umbilical cord blood	3.4	Myeloablative	No		CyA/MTX
14	Female	37	AML	1st CR	Matched related	Peripheral blood	11.5	Myeloablative	No		CyA/MTX
4	Female	63	MCL	1st CR	Matched related	Peripheral blood	12.2	Reduced intensity	Yes	2	CyA/MMF

LGL indicates large granular lymphocytes; HSCT, hematopoietic stem cell transplant; TBI, total body irradiation; GVHD, graft-versus-host disease; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; CyA, cyclosporine A; MMF, mycophenolate mofetil; SAA, severe aplastic anemia; ATG, antithymocyte globulin; BM, bone marrow; MTX, methotrexate; CR, complete remission; NK, natural killer cells; TL, T cell lymphoma; CML, chronic myeloid leukemia; DLBCL, diffuse large B cell lymphoma; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; PMF, primary myelofibrosis; MCL, mantle cell lymphoma.

expansions had relevant clinical signs such as cytopenia with septicemia, polyarthritis, or granulomatous hepatitis. In solid organ transplant setting, T-LGL expansion is even more frequent. It was reported in 18 of 23 solid organ transplant recipients, without signs of rejection, infection, or signs of T-LGL leukemia [16]. As for our cohort, T-LGL expansions, even of clonal origin, were without clinical manifestations.

In treated CMV infection, clonal expansion of T-LGL can last up to several months [4]. After solid organ transplant with CMV infection, an LGL expansion may appear more than 6 months later and persist up to several years [17]. These data are consistent with our finding that there was a correlation between CMV reactivation and LGL expansion even in patients with a very long-term follow-up. Thus, 7 of 9 patients with LGL expansion cleared the virus at study time. Two of 9 patients had multiple reactivation of viral replication along the post-HSCT follow-up time. Seven of 9 patients needed therapy to control the replication. One patient had CMV colitis. The median time between the last positive replication and the study time was 56 months (range, 0-159 months).

Data from the literature about the relationship between CMV reactivation, GVHD, and LGL expansion after allogeneic HSCT are conflicting. Some of them described an association of T-LGL with CMV infection and GVHD [18], whereas other data showed only an association with CMV infection [19]. In our cohort, LGL expansion was associated with CMV replication but not with aGVHD. All patients were classified as LGL expansions and not as T cell LGL leukemia. At first, this seems to be in contradiction with a number of case reports on T-LGL leukemia after HSCT [7,20-25]. Our results cannot exclude that LGL expansion may rarely evolve into T-LGL leukemia after HSCT. However, these cases remain the exception compared to the relative high number of patients with T-LGL expansions.

In conclusion, we observed T-LGL expansion in 7% of a large cohort of post-HSCT survivors. The majority of the LGL expansions presented with a CD3+/CD8+ phenotype, and 36% had a clonal TCR gene rearrangement. Regardless of clonality, all patients were clinically asymptomatic with respect to T-LGL expansion. Our data indicate that, even if monoclonal, posttransplantation T-LGL expansion may be considered as an expression of chronic stimulation triggered by CMV reactivation rather than the result of a malignant transformation. Whether the presence of LGL expansion is the expression of a balanced chronic immune response with a possible graft-versus-leukemia effect after allogeneic HSCT should be evaluated in a larger cohort of patients.

Table 3. Posttransplantation Data

Patient	aGVHD (Grade)	cGvHD	Current IS	CMV Replication	Time between HSCT and T-LGL Diagnosis (Months)	Lymphocyte Count (G/L)	T-LGL Count (G/L)	Immunophenotype of T-LGL Expansion	TCR-gamma Gene Rearrangement	Alive/Dead Follow-up (Months)
8	1	Extensive	Yes	No	22	3.04	2.130	CD2/CD3/CD5/CD7/CD8/HLADR/CD16/CD57/TCRab/CD56−	Clonal	Alive 53
6	No	No	No	No	1.5	4.3	2.039	CD2/CD3/CD5/CD7/CD8/HLADR/CD16/CD57/TCRab/CD56−	Clonal	Alive 61
12	2	Extensive	Yes	Yes	3	3.0	2.652	CD2/CD3/CD7/CD8/CD16/CD57/TCRab/CT56−	Clonal	Alive 8
9	No	Extensive	Yes	Yes	1.5	24.0	11.528	CD2/CD3/CD5/CD7/CD8/HLADR/CD57/TCRab/CD16−/CD56− and CD2/CD3/CD4/CD5/HLA-DR/CD57/TCRab/CD16−/CD56−	Clonal	Dead 18
13	2	No	Yes	Yes	12	3.77	3.619 2.109	CD2/CD3/CD5/CD7/CD8/HLADR/CD16/CD57/TCRab, CD56−	Biclonal	Alive 13
1	2	Limited	No	Yes	7	5.68	2.629	CD2/CD3/CD8/CD57 CD16/TCRab/CD56−	Polyclonal	Alive 162
2	2	Limited	No	No	24	4.09	1.252	CD2/CD3/CD5/CD7/CD8/CD57/TCRab/CD16−/CD56−	Polyclonal	Alive 146
3	3	Limited	No	Yes	150	4.96	1.934	CD2/CD3/CD8/CD57/TCRab/ CD16-/CD56−	Polyclonal	Alive 61
5	3	Extensive	Yes	Yes	24	3.36	1.286	CD2/CD3/CD5/CD7/CD8/HLADR/CD16/CD56/CD57/TCRab	Polyclonal	Alive 86
7	No	Extensive	Yes	Yes	58	4.36	2.168	CD2/CD3/CD5/CD7/CD8/HLADR/CD56/CD57/TCRab/CD16−	Polyclonal	Alive 71
10	3	Extensive	No	Yes	23	3.8	1.692	CD2/CD3/CD5/CD7/CD8/CD16/CD57/TCRab/CD56−	Polyclonal	Alive 37
11	2	No	No	No	9	4.17	1.513	CD2/CD3/CD5/CD7/CD8/CD16/CD57/TCRab/CD56−	Polyclonal	Alive 29
14	2	No	Yes	No	6	4.49	2.745	CD3/CD5/CD7/CD8/HLA-DR/CD16/CD57/TCRab/CD56−	Polyclonal	Alive 3
4	3	Extensive	Yes	Yes	12	6.53	2.086	CD3/CD4/CD56/CD57/TCRab/CD16−	Polyclonal	Alive 85

aGVHD indicates acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; IS, immunosuppression; CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplant; T-LGL, T cell large granular lymphocyte.

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SUPPLEMENTARY DATA

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